

## **Section II (Remarks)**

### **Amendment to the Claims**

In the claims, new claims 13-15 have been added, claims 1, 7 and 12 have been amended, and claim 11 has been cancelled.

Claims 1 and 7 have been amended to depend from claim 8, and claim 12 has been amended to add a period at the end of such claim.

New claim 13 recites a method of producing 17a-acetoxy-11b-(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione (VA-2914), comprising providing VA-2914 isopropanol hemisolvate; and desolvating the VA-2914 isopropanol hemisolvate, to convert VA-2914 isopropanol hemisolvate to VA-2914. New claim 14 is of dependent form under claim 13 and recites that the desolvating comprises recrystallizing VA-2914 isopropanol hemisolvate in a solvent selected from the group consisting of ethanol/water solvent and ethylether solvent.

Claim 15 is of corresponding form to claim 2, but depends from claim 8, while claim 2 depends from claim 1.

New claims 13-15 are fully consistent with and supported by the original disclosure of the application and involve no new matter (35 USC 132).

### **Priority Claim**

The Office Action at page 2 thereof acknowledges the priority claim to Spanish patent application P200300162 filed January 22, 2003, but requests a certified copy of such application. In response, it is pointed out that the present application is a 371 US national phase of PCT/ES04/00026 filed January 21, 2004 which in turn claims the priority of Spanish patent application P200300162 filed January 22, 2003. Attached in Appendix A of this response is a copy of the Form PCT/IB/304 issued by the International Bureau reporting the receipt of the

priority document. Accordingly, the priority has been established in the international proceedings of the present US national phase application.

Applicants additionally are procuring a certified copy of the priority document, and same will be hereafter submitted, to complete the record of this application.

#### **Rejection of Claim 11 Under 35 USC 101**

The rejection of claim 11 as originally filed in this US national phase has been rendered moot by the cancellation of such claim herein.

#### **Rejection of Claims 11 and 12 Under 35 USC 112, Second Paragraph**

In the November 26, 2008 Office Action, claims 11 and 12 were rejected under 35 USC 112, second paragraph as indefinite. Claim 11 was rejected as lacking positively recited method steps. As mentioned in the preceding sub-section of these Remarks, claim 11 has been cancelled herein. The rejection of claim 11 is therefore rendered moot.

New claim 14 has been added, directed to a method of producing VA-2914 comprising the step of “desolvating the VA-2914 isopropanol hemisolvate, to convert VA-2914 isopropanol hemisolvate to VA-2914.” Such added method claim therefore fully complies with the requirements of 35 USC 112, second paragraph.

Claim 12 has been rejected as lacking a period at the end of such claim. Claim 12 has correspondingly been amended herein to place a period at the end of such claim.

#### **Double Patenting Rejection of Claim 12 Under 35 USC 101**

Claim 12 was provisionally rejected in the November 26, 2008 Office Action as claiming the same invention as claim 25 in copending application 10/542,580.

It is noted that US Patent Application 10/542,580 is not owned by the assignee of the present application, but rather derives from an international patent application PCT/US04/04246 filed on February 13, 2004 claiming the priority of US Provisional Patent Application No. 60/451,096 filed February 28, 2003. As discussed earlier herein, the examiner has acknowledged applicants' priority claim to Spanish patent application P200300162 filed January 22, 2003. Applicants' priority date of January 22, 2003 thus antedates the February 28, 2003 filing date of the cited reference.

It therefore is requested that the provisional rejection of claim 12 on double patenting grounds be withdrawn.

**Rejection of Claims 1, 5, 8, 9 and 11 Under 35 USC 102(b) Over Kim et al.**

In the November 26, 2008 Office Action, claims 1, 5, 8, 9 and 11 were rejected under 35 USC 102(b) over Kim et al. WO96/30390 ("Kim").

It is noted that claim 1 has been made dependent on claim 8, and that claim 11 has been cancelled herein.

Independent claim 8 recites a process for purifying raw VA-2914 (17 $\alpha$ -acetoxy-11 $\beta$ -(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-diene-3,20-dione) which involves its recrystallization in isopropanol to form its isopropanol hemisolvate. The process and the isopropanol hemisolvate are novel.

Kim et al. describes a process for the preparation of 17 $\alpha$ -acetoxy-11 $\beta$ -(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-dien-3,20-dione (VA-2914) which includes a purification step through crystallization in ether (p. 15, l. 9-22). The purification process is detailed in Example 7 (p. 23, l. 26-33). The Kim process comprises the following steps:

- a) dissolving compound VA-2914 obtained as a syrup in isopropanol and subjecting the solution to evaporation (this step is repeated 3 times);

- b) the solid obtained, which still contains isopropanol as crystallization solvent, is dissolved in ethyl acetate and evaporated to provide a stable foam;
- c) the foam is dissolved in ether and recrystallized from ether; and
- d) the solid obtained is recovered by filtration, washed with ether and dried *in vacuo* to obtain VA-2914 as yellow crystals with a melting point of 183-185 °C.

Therefore, applicants' process of **Claim 8** differs from that of Kim et al., since applicants' process involves recrystallization of VA-2914 in isopropanol to obtain the corresponding hemisolvate. By contrast, Kim only describes evaporation of the solvent (isopropanol) to dryness to obtain a foam (see example 7 of Kim) and not recrystallization to afford hemisolvate crystals. In Kim, a recrystallization from ether is described. Therefore, claim 8 is novel over Kim, and it is correspondingly requested that the rejection of claim 8 over Kim be withdrawn.

Consequently, **claims 1 and 5**, dependent on claim 1, also fulfill the novelty requirement.

**Claim 9** recites 17 $\alpha$ -acetoxy-11 $\beta$ -(4-N,N-dimethylaminophenyl)-19-norpregna-4,9-dien-3,20-dione (VA-2914) isopropanol hemisolvate. This compound is not disclosed by Kim et al., since Kim does not describe the preparation of VA-2914 isopropanol hemisolvate after crystallization in isopropanol, but the formation through evaporation of a solid which retains solvent.

As indicated, **claim 11** has been cancelled, and the rejection is moot as to such claim.

New **claim 14** defines a method of purifying VA-2914 comprising desolvating the VA-2914 isopropanol hemisolvate. As already mentioned, Kim et al. does not disclose VA-2914 isopropanol hemisolvate and, therefore, it does not anticipate a further synthetic step using such hemisolvate.

New **claim 15** depends on claim 14 and, therefore, is also novel over Kim.

**Rejection of Claims 2-4, 6, 7, 10 and 12 Under 35 USC 103(a)**

Claims 2-4, 6, 7, 10 and 12 were rejected under 35 USC 103(a) in the November 26, 2008 Office Action, as unpatentable over Kim in view of Cook.

Kim discloses a purification process for 17 $\alpha$ -acetoxy-11 $\beta$ -(4-*N,N*-dimethylaminophenyl)-19-norpregna-4,9-dien-3,20-dione comprising steps a)-d) mentioned above, see *supra*. The final product VA-2914 obtained using such process has a yellow colour (example 7), which is indicative of the presence of impurities (mainly of phenolic origin).

As discussed hereinabove, the applicants' process of **claim 8** differs from Kim et al. in that VA-2914 is recrystallized from isopropanol, and not from ether. In this way, white crystals are obtained, an indication of the absence of impurities. Additionally, a higher melting point (189°C vs. 183-185°C in Kim et al.) is achieved, which is a clear proof of enhanced purity.

Hence, the process specified in applicants' **claim 8** solves the problem of providing an improved purification process for the compound 17 $\alpha$ -acetoxy-11 $\beta$ -(4-*N,N*-dimethylamino-phenyl)-19-norpregna-4,9-dien-3,20-dione (VA-2914) in a manner so that such compound is obtained in a higher purity grade than those obtained to date.

The process of **claim 8** therefore enables purification of VA-2914 to be achieved by formation of VA-2914 isopropanol hemisolvate crystals through crystallization of VA-2914 in isopropanol. As described in the instant patent application, VA-2914 purified by such process is obtained as white crystals (vs. the yellow colored crystals obtained by the method of Kim) having a higher melting point [189°C vs. 183-185°C in Kim et al.]. Thus, the process of the present invention, as broadly set forth in claim 8, provides crystals of a net superior purity.

This solution for achieving high purity VA-2914, involving recrystallization from isopropanol, would not have been obvious to a skilled person, since the art does not suggest the formation of VA-2914 isopropanol hemisolvate to purify VA-2914. Furthermore, it would not have been predicted that such process of applicants' invention would improve the purity of the final product in relation to the purification process disclosed in Kim.

Cook describes steroids of similar structure to VA-2914, which display antiprogestational and antigluccorticoidal activity, as well as a process for obtaining such compounds. Cook, however, does not describe any purification methods or processes for obtaining said steroids through the crystallization of such compounds in isopropanol or the formation of isopropanol hemisolvates.

For the foregoing reasons, applicants' claimed process as broadly set out in **claim 8** finds no derivative basis in the reference combination of Kim in view of Cook.

**Claims 2-4, 6 and 7** are of dependent form under **claim 8**, and are therefore likewise distinguished over Kim in view of Cook.

**Claim 10**, which recites the process of obtaining VA-2914 isopropanol hemisolvate, is not obvious over Kim in view of Cook, for the same reasons as mentioned above, i.e., Kim only describes an evaporation process, and not a crystallization process to yield hemisolvate crystals.

Additionally, this claim is directed to a new process of preparation of a new and inventive compound (isopropanol hemisolvate according to claim 9) and therefore it also is necessarily non-obvious.

**Claim 12**, which recites 3,3-(1,2-ethanedioxy)-5 $\alpha$ -hydroxy-11 $\beta$ -(4-*N,N*-dimethylaminophenyl)-17 $\alpha$ -acetoxy-19-norpregna-9-en-20-one (carbinol acetate), a precursor of VA-2914, is also non-obvious over the Kim in view of Cook combination. The Office Action at page 6 thereof acknowledges that claim 12 differs from Kim in reciting such compound, but Cook has been cited as teaching similar compounds. Cook, however, fails to disclose such carbinol acetate compound and it therefore is new over the cited prior art. Carbinol acetate recited in claim 12 has been found to be useful in the preparation of VA-2914 with an improved purity. Consequently, this compound is considered an inventive intermediate of an overall inventive process.

It therefore is requested that the 35 USC 103(a) rejection of claims 2-4, 6, 7, 10 and 12 be withdrawn.

**Fee Payable for Added Claims 13-15**

The addition of new claims 13-15 does not increase the number of independent claims, or total claims, beyond the numbers for which payment has been previously made. Accordingly, no added claims fee is due.

If it nonetheless is determined that any additional fee or amount is payable, authorization is hereby given to charge the amount thereof to Deposit Account No. 08-3284 of Intellectual Property/Technology Law.

**CONCLUSION**

In light of the above remarks, it is requested that the rejection of claims 1-10 and 12 be withdrawn, and that the patentability of claims 13-15 likewise be acknowledged. All of Applicants' pending claims 1-10 and 12-15 are now patentably distinguished over the art, and in form and condition for allowance. The examiner is requested to favorably consider the foregoing, and to responsively issue a Notice of Allowance. If any issues require further resolution, the examiner is requested to contact the undersigned attorney at (919) 419-9350 to discuss same.

Respectfully submitted,

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